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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/433,777	11/03/1999	JOEL R. HAYNES	APF-18.20	2990

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/433,777	HAYNES ET AL.	
	Examiner	Art Unit	
	Anne M Wehbé	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *6,8-11,13,14 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,12,15-25 and 29-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response received on 6/7/02 has been entered. Claims 27-28 have been canceled. Claims 1-26 and 28-47 are pending in the instant application. Of these, claims 6, 8-11, 13-14, and 26 have been withdrawn from consideration as being drawn to subject matter non-elected without traverse in paper no. 7. Please note that a complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-5, 7, 12, 15-25, and 29-47 are therefore under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejections of claims 27 and 28 under 35 U.S.C. 112, second paragraph, and 35 U.S.C. 101 are withdrawn in view of applicant's cancellation of the claims

The rejection of pending claims 1, 16, and 29-47 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained over claims 1, 16, and 33-47. Applicant's arguments have

been fully considered but have not been found sufficient in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the rejection of record focuses on one embodiment of the claimed invention, wherein the claimed compositions include an "immune shift lipid adjuvant", and that the office has not given sufficient weight to applicant's working examples which utilize non-lipid adjuvants. In response, please note that the applicant has previously elected the species of "lipid adjuvants" for prosecution in the instant application. Further, the rejection of record is concerned with the lack of enablement provided by the specification for shifting the immune response from Th1 to Th2 or vice versa using any lipid adjuvant. This rejection does not state that the specification is not enabling for method of generating immune responses to antigen using the disclosed compositions of DNA and non-DNA lipid adjuvants. The rejection of record is specifically concerned with the lack of enablement for using lipid adjuvants with are capable of "shifting" the immune response. The applicant has defined the term "immune shift" as meaning a shift in the immune response from a Th1 response to a Th2 response or vice versa, see specification page 14, lines 19-27. Therefore, by the applicant's own definition of the term, claims reciting an "immune shift" require more than simply generating or enhancing an immune response to an antigen. The term "immune shift" has patentable weight in the claims in terms of enablement, and is particularly claimed in claims 16, and 33-47. Claim 1 has been included in this rejection as claim 16 depends on claim 1. As such, it is proper to consider whether the

specification provides an enabling disclosure for this particularly claimed limitation of the instant invention.

The applicant further argues that the previous office action focused on the results obtained in the specification working example which uses MPL adjuvant combined with DNA encoding a CEA antigen, and does not take into account applicant's working examples which utilize antigens from HIV or hepatitis B in combination with Quil A. Please note that the applicant has elected the species of "lipid" adjuvants for prosecution in the instant application. Quil A is a saponin adjuvant, not a lipid adjuvant. Therefore, data regarding the use of Quil A as the non-DNA adjuvant concerns subject matter non-elected in the instant application. The issue at hand is whether the specification provides an enabling disclosure for lipid based adjuvants. Thus, the relevant working example in the specification is the working example where the applicants tested compositions comprising monophosphoryl lipid A and DNA encoding CEA. The previous office action analyzed the working example which uses a lipid adjuvant as follows. The specification provides a working example of the instant invention which demonstrates that co-administration of gold beads coated with monophosphoryl lipid A (MPL) and gold beads coated with a DNA plasmid vector encoding the carcinoembryonic antigen (CEA) under transcriptional control of the CMV promoter to the epidermis of Balb/C mice by particle-mediated bombardment results in a decrease in the ratio of CEA specific IgG1 to IgG2a in mouse serum compared to the administration of CEA-plasmid alone. The specification provides no data concerning the T helper cytokine patterns or level of anti-CEA cytotoxicity in the vaccinated mice. The specification suggests that this

decrease in the IgG1/IgG2a ratio correlates to a shift in the T helper phenotype of the mouse's immune response to CEA from a Th2 to a Th1 type response. However, it is clear that the applicant's data does not demonstrate a "shift" from Th2 to Th1 since the overall ratio of IgG1 to IgG2a shows that the predominant isotype is IgG1 rather than IgG2a which indicates a Th2 type response. The applicant's data therefore only demonstrates a decrease in the magnitude of the T helper response rather than an actual shift. Thus, the skilled artisan would not find the specification's working example evidence that the co-administration of MPL shifts the immune response generated against CEA from a Th2 type response to a Th1 type response as the mice continue to exhibit primarily IgG1 anti-CEA antibodies. The applicant has not refuted these findings.

In regards to applicant's argument that the working examples utilize an art-recognized mouse model and that human clinical data is not required, please note that the previous office action did not require human clinical data and did **not** state that the mouse model was not suitable for exemplifying immunological compositions. The applicant has misunderstood the grounds of rejection. The previous office action explained in some detail that T helper subsets have not been fully characterized for any species other than mouse, and that it was clearly known in the prior art at the time of filing that different strains of inbred mice appeared to respond differently to antigens in terms of the generation of Th1 versus Th2 responses (Golding et al., Abbas et al.). In analyzing the applicant's working example, the office simply pointed out that the applicant's working example where Balb/C mice were injected with gold beads coated with monophosphoryl lipid A

and a plasmid encoding CEA did not in fact demonstrate any actual "immune shift" from Th1 to Th2, and that based on the known differences in T helper responses to antigen observed in different strains of mice, the skilled artisan would not have been able to predict whether monophosphoryl lipid A would be capable of causing an "immune shift" to an antigen in any species of mouse or other mammals.

In regards to the applicant's argument that the office has not met its burden to provide a reasonable basis to question the enablement of the instant specification for the elected subject matter, citing *In re Wright* and *In re Marzocchi*, it is noted that the previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. Further, case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Finally, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).Therefore, due to the art recognized complexity and unpredictability of shifting the T helper immune response to a pathogenic antigen in mammals, the breadth of the claims, and the lack of sufficient guidance from the specification concerning vector

and promoter selection, level of antigen expression, genetic background of the mammal to be vaccinated, and routes of administration in regards to their affect on a) generating a particular T helper response in the absence of adjuvant and b) the ability of a particular lipid adjuvant to shift that T helper response to either Th1 or Th2, it would have required undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The rejection of pending claims 1-2, 7, 12, 15, 27-29, 33, 35, 37, 39, 41, 43, and 46-47 under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent No. 5,925,362, hereafter referred to as Spitler et al., is maintained. Applicant's arguments have been fully considered but have not been found sufficient in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the office has misconstrued the teachings of Spitler et al. The applicant states that in columns 7-9 of the Spitler et al. patent, the disclosure refers to the combination of protein/peptide PSA antigens and liposomal adjuvants, and does not actually teach the combination of nucleic acid sequences encoding PSA in combination with non-DNA adjuvants. Based on applicant's analysis of the Spitler specification, the applicant concludes that Spitler never contemplated applicant's claimed combination of nucleic acid and non-DNA adjuvant. This interpretation of the teachings of Spitler et al. is clearly incorrect. Claim 1 of the

Spitler patent recites a method of eliciting an antitumor immune response to prostate tumors in a subject comprising administering to said subject an active ingredient comprising either human PSA, or an expression system capable of generating in situ said human PSA. Claim 5, which depends on claim 1, clearly recites wherein the active ingredient is formulated to be encapsulated in a liposome or coupled to a liposome and wherein said liposomes optionally contain an adjuvant. Claim 6 also recites the method of claim 1 which further includes at least one adjuvant capable enhancing said antitumor immune response. Claim 7, which depends on claim 6, recites a list of adjuvants which include monophosphoryl lipid A. Since the claims clearly recite the combination of **either** a protein PSA antigen or an expression system capable of generating in situ said PSA and an adjuvant such as monophosphoryl lipid A, there can be no doubt that Spitler et al. contemplated applicant's claimed combination of nucleic acid encoding an antigen and non-DNA adjuvant. Furthermore, contrary to applicant's analysis of the teachings of columns 7-8, column 8, lines 9-12, clearly states that as an embodiment of the instant invention recombinant vectors included in a liposome injectable "as described above" can be administered to the subject. The description of liposome injectables referenced in column 8 can be found in column 7 which clearly teaches that liposomes may also include immune system adjuvants such as lipid A. Thus, it is clear from both the teachings of the specification and the claims of the 5,925,362 patent, that Spitler et al. teaches all the elements of the applicant's invention. As such, Spitler et al. anticipates the invention as claimed.

Please note as well that the previous office action stated that while Spitler et al. does not specifically teach that monophosphoryl lipid A "shifts" the immune response to PSA, case law states that "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The applicant is reminded that the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim Rejections - 35 USC § 103

The rejection of claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42, 44-45 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,925,362, hereafter referred to as Spitler et al., in view of Fynan et al., Golding et al., and Sedegah et al. is maintained. Applicant's arguments have been fully considered but have not been found sufficient in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the office has not met the requirements set forth in section 2143 of the MPEP for establishing *prima facie* obviousness over the applicant's claimed invention. The applicant's reason for this conclusion is based on applicant's contention that the primary reference Spitler et al. does not teach or suggest applicant's claimed combination of a DNA encoding an antigen and a non-DNA adjuvant. The applicant has not provided any actual arguments traversing the teachings of Fynan, Golding, or Sedegah as applied in the instant rejection. The applicant's arguments concerning the teachings of Spitler et al. are discussed in detail above in the response to applicant's arguments concerning the teachings of Spitler et al. under 35 U.S.C. 102(e). In brief, the office finds that in particular claims 1, and 5-7 of the Spitler et al. patent clearly recite the combination of an expression system encoding a PSA antigen and a non-DNA adjuvant such as monophosphoryl lipid A for use in generating anti-tumor immune responses in vivo in a subject. Therefore, the office submits that the previous office action did in fact follow the three basic requirements for *prima facie* obviousness as required by section 2143 of the MPEP.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER